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| 09/782,361 | 02/13/2001 | Yu-Wen Hu | 4757US | 1070 |

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| EXAMINER |
|---|
| STRZELECKA, TERESA E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | 23 |

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/782,361 | HU, YU-WEN | |
| | Examiner | Art Unit | |
| | Teresa E Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12,14,15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14,15 and 17-26* is/are rejected.

7)☒ Claim(s) *1 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *22* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This Office action is in response to an amendment filed on March 26, 2003. Claims 1-12, 14, 15, 17-22 were previously pending. Applicants amended claims 9, 14 and 15, and added new claims 23-26. Applicants' amendment overcame the rejection of claims 9, 14 and 15 under 35 U.S.C. 112, second paragraph. Claims 1-12, 14, 15 and 17-26 are pending and will be examined.

2. This office action is made non-final because of new grounds for rejection.

### *Claim Objections*

3. Claim 1 is objected to because of the following informalities: "using a primer-specific for a genotype" in line 4. Appropriate correction is required.

4. Claim 20 is objected to because of the following informalities: "using a primer-specific for a genotype" in line 4. Appropriate correction is required.

5. Claim 20 is objected to because of the following informalities: ddNPTs repeated twice in line 5. Appropriate correction is required.

### *Remarks concerning the art rejections*

6. The art rejections presented below are based on the following interpretation of claims 1, 20, 23 and 24: the recitation of "... said one or more extension products are terminated in the presence of at least two mispairs within 2 to 4 base pair range located downstream of the 3' end of the primer..." in step a) of claims 1 and 23 and the recitation of "... wherein an extension product is prevented when a mispair occurs at at least one of a first or second base pair immediately adjacent to the 3' end of the primer..." in step a) of claims 20 and 24. These phrases characterize function performed by step a), related to the property of the pfu polymerase, but are not by themselves active method steps.

***Claim Rejections - 35 USC § 102/103***

7. Claims 1-11, 14, 15 and 17-26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fahy (WO 96/30545; previously cited) and Lundberg et al. (Gene, vol. 108, pp. 1-6, 1991).

Regarding claims 1, 2, 14, 15 and 20-26, Fahy teaches a method of simultaneous determination of related polynucleotide sequences, for example, within the same gene, in a nucleic acid sample by:

- providing a nucleic acid sample from a patient (page 29, lines 17-37; page 30, lines 1-30),
- extending a primer specific for the genotype by Pfu (= pfu) DNA polymerase (page 19, lines 36, 37; page 20, lines 3-34), and an incomplete set of dNTP's (at most three) in the absence of ddNTPs (page 7, lines 18-37; page 18, lines 26-32), where the primer is labeled with fluorescent label (page 8, lines 12-14),
- characterizing the extension products by separating the extension products based on their lengths (page 21, lines 2-14; Fig. 5A-C),
- analyzing the characterized extension products based on primer-specific pairing and non-specific pairing to determine genotype of the extended nucleic acid sequence and generating a genotype-specific extension profile of the extension products (page 34, lines 26-37; page 35, lines 1-11; Table IA and IB; Fig. 8; Fig. 4A and 4B).

Regarding claim 2, Fahy teaches characterization of the extension products by comparing lengths of the extension products using size separation methods, including gel electrophoresis, capillary electrophoresis or mass spectrometry (page 21, lines 2-14).

Regarding claim 3, a target nucleic acid from a sample is amplified before the extension (page 17, lines 22-35).

Regarding claims 4 and 5, two or three dNTPs are used in primer extension (page 18, lines 26-32).

Regarding claim 6, Fahy teaches labeled primers (page 8, lines 12-14; page 21, lines 23-26) and labels which are fluorescent, luminescent or radioactive (page 15, lines 34-37; page 16, lines 1-3).

Regarding claim 7, dNTPs used for extension are labeled (page 21, lines 27-31) and labels which are fluorescent, luminescent or radioactive (page 15, lines 34-37; page 16, lines 1-3).

Regarding claims 9, 10 and 11, extension products are analyzed on an automated sequencer, where they are sequenced with BioImage Analyzer software (page 34, lines 13-32).

B) Regarding claims 1, 17-19, 20, 23 and 24, Fahy does not teach termination of extension products in the presence of at least two mispairs within a 2 to 4 base pair range located downstream of the 3' end of the primer or termination of extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer. However, the position of a mispair formation with respect to the 3' end of the primer is dependent on the template sequence and type of dNTPs present in the reaction mixture, and is inherently related to the fact that Pfu polymerase is a high-fidelity polymerase.

C) The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594, because Fahy et al. is silent with respect to the fact that Pfu polymerase terminates primer extension at a distance determined by the type on dNTPs present in the reaction and template sequence. However, termination of extension products in the presence of at least two mispairs within a 2 to 4 base pair range located downstream of the 3' end of the primer or termination of

extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer recited in claims 1, 17-19, 20, 23 and 24 are deemed to be inherent in the property of the high-fidelity in the Pfu polymerase in Fahy (page 20, lines 3-34) because of teachings of Lundberg et al., described below.

Lundberg et al. teach testing proofreading ability of Pfu polymerase by extension of a primer with one, two or three mismatches at the 3' end of the primer. All of the primers were extended and mismatched nucleotides were excised by the 3'->5' exonuclease activity of the polymerase (Fig. 1; page 2, paragraph (b)). Following Figure 1b, it is clear that if only dTTP and dGTP, for example, were included in the reaction mixture, mispair would have occurred at the second base from the 3' end of the primer, and extension would have been terminated there. If only dTTP and dCTP, for example, were included in the reaction mixture, mispair would have occurred at the third base from the 3' end of the primer, and extension would have been terminated at this position. If only dTTP and dATP, for example, were included in the reaction mixture, mispair would have occurred at the second and third base from the 3' end of the primer, and extension would have been terminated there.

D) In the alternative, it is obvious that termination of primer extension at a certain distance from the 3' end of the primer is an inherent property of the Pfu DNA polymerase under reaction conditions where an incomplete set of dNTPs is present in the reaction mixture. Fahy teaches the high-fidelity the Pfu polymerase (page 20, lines 3-34) and Lundberg et al. teach testing proofreading ability of Pfu polymerase by extension of a primer with one, two or three mismatches at the 3' end of the primer. All of the primers were extended and mismatched nucleotides were excised by the 3'->5' exonuclease activity of the polymerase (Fig. 1; page 2, paragraph (b)). Following Figure 1b, it is clear that if only dTTP and dGTP, for example, were included in the

reaction mixture, mispair would have occurred at the second base from the 3' end of the primer, and extension would have been terminated there. If only dTTP and dCTP, for example, were included in the reaction mixture, mispair would have occurred at the third base from the 3' end of the primer, and extension would have been terminated at this position. If only dTTP and dATP, for example, were included in the reaction mixture, mispair would have occurred at the second and third base from the 3' end of the primer, and extension would have been terminated there.

Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention that Pfu polymerase would have terminated primer extension at different positions relative to the 3' end of the primer in a fashion dependent on the template sequence and type of dNTPs included in the incomplete dNTP set. The termination would occur because Pfu possesses proofreading function.

The burden is on applicant to show that the termination of extension products in the presence of at least two mispairs within a 2 to 4 base pair range located downstream of the 3' end of the primer or termination of extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer is either different or non-obvious over that of Fahy.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 12 (SEQ ID NO: 2, 6, 7) is rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy, Lundberg et al. and Resnick et al. (U.S. Patent No. 5,527,669; previously cited).

A) Claim 12 is drawn to an assay of claims 1 and 2, with a primer selected from the group consisting of SEQ ID NO: 1-15.

B) Teachings of Fahy and Lundberg et al. have been described above. Fahy teaches that the genotyping method can be applied to detection of multiple mutations in viral nucleic acid (HIV-1). Neither Fahy nor Lundberg et al. teach primers selected from the group consisting of SEQ ID NO: 1-15.

C) Resnick et al. teach oligonucleotide primers which can be used to amplify and detect HCV nucleic acids. Primers with SEQ ID NO: 8, 15 and 18 (overlapping with SEQ ID NO: 6, 7 and 2, respectively) can be used to amplify HCV genotypes from Japan , USA and HCV-C9 (col. 27, lines 57-66).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the HCV detection primers of Resnick et al. in the combined method of Fahy and Lundberg et al. The motivation to do so, provided by Resnick et al., would have been that these primers allowed amplification of a large number of HCV strains (col. 27, lines 57-66).

10. Claim 12 (SEQ ID NO: 4) is rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy, Lundberg et al. Okamoto (U.S. Patent No. 5,550,016; previously cited).

A) Claim 12 is drawn to an assay of claims 1 and 2, with a primer selected from the group consisting of SEQ ID NO: 1-15.

B) Teachings of Fahy and Lundberg et al. have been described above. Fahy teaches that the genotyping method can be applied to detection of multiple mutations in viral nucleic acid (HIV-1). Neither Fahy nor Lundberg et al. teach primer with SEQ ID NO: 4.

C) Okamoto teaches oligonucleotide primers which can be used to amplify and detect different HCV strains. Primer with SEQ ID NO: 18 (overlapping with SEQ ID NO: 4) can be used to detect HCV strains I-VI (col. 3, lines 34-39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the HCV detection primer of Okamoto in the in the combined method of Fahy and Lundberg et al. The motivation to do so, provided by Okamoto, would have been this primer was used to detect multiple HCV strains (col. 3, lines 34-39).

11. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
July 24, 2003

JAMES FORMAN, PH.D.
PRIMARY EXAMINER